510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY TEMPLATE

A. 510(k) Number

K040887

B. Purpose for Submission:

Substantial equivalence

C. Measurand:

Procalcitonin (PCT**)**

D. Type of submission

Immunoluminometric assay, semi quantitative

E. Applicant:

BRAHMS Diagnostica, LLC

F. Proprietary and Established Names:

BRAHMS PCT LIA

G. Regulatory Information:

1. Regulation section:

   21 CFR Part 866.3610, Endotoxin activity

2. Classification:

   Class II

3. Product code:

   NTM - Antigen, inflammatory response marker, sepsis

4. Panel:

   Microbiology (83)

H. Intended Use:

1. Intended use(s):

   The BRAHMS PCT LIA is an immunoluminometric assay used to determine the concentration of procalcitonin (PCT) in human serum and plasma. The BRAHMS PCT LIA is intended for use in conjunction with other laboratory findings and clinical assessments to aid in the risk assessment of critically ill patients on their first day of ICU admission for progression to severe sepsis and septic shock.

2. Indication(s) for use:

   BRAHMS PCT LIA is indicated for use in conjunction with other laboratory findings and clinical assessments to aid in the risk assessment of critically ill patients on their first day of ICU admission for progression to severe sepsis and septic shock.

3. Special conditions for use statement(s):

   Prescription use

4. Special instrument requirements:

   Luminometer

I. Device Description:

The BRAHMS PCT LIA kit contains reagents for 100 determinations. The contents of the kit are luminescence labeled tracer, buffer solution, test tubes coated with anti-PCT antibody (monoclonal mouse) ready for use, zero serum for reconstituting the standards and controls, universal washing solution, PCT standards and controls

J. Substantial Equivalence Information:

1. Predicate device name:

   Endotoxin Activity Assay (EAA)

2. Predicate 510(k) number:

   K021885

3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Label	Chemiluminescence	Chemiluminescence
Reader	Luminometer	Luminometer

Differences		
Item	Device	Predicate
Specimen	Serum or plasma	Whole blood
Format	The relative light unit (RLU) signal is proportional to PCT in the sample	RLU measured by the instrument is converted by calculation into an endotoxin activity value
Standards	Six standards used in the assay	None
Analyte	Measures procalcitonin concentration	Measures endotoxin activity

K. Standard/Guidance Document Referenced (if applicable):

NCCLS EP6-P "Evaluation of the Linearity of Quantitative Analytical Methods".

L. Test Principle:

B·R·A·H·M·S PCT LIA is an immunoluminometric assay (ILMA) used to determine the concentration of Procalcitonin (PCT) in human serum and plasma. Two antigen-specific monoclonal antibodies that bind PCT (the antigen) at two different binding sites (the calcitonin and katacalcin segments) are added in excess. One of these antibodies is luminescence labeled (the tracer), and the other is fixed to the inner walls of the tube (coated tube system).

During the course of incubation, both antibodies react with PCT molecules in the sample to form "sandwich complexes". As result the luminescence labeled antibody is bound to the inner surface of the tube. Once the reaction is completed, the excess tracer is completely removed from the tube and discarded.

Then, the amount of residual tracer on the test tube wall is quantified by measuring the luminescence signal using a suitable luminometer and the B·R·A·H·M·S Basiskit LIA reagents. The intensity of the luminescence signal (RLU) is directly proportional to the PCT concentration in the sample. After a standard curve has been established using standards with known antigen concentrations (calibrated against recombinant intact human PCT), the unknown PCT concentrations in patient serum or plasma samples can then be quantitated by comparison of test values with the curve.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

Aliquots of 14 samples distributed over the measuring range were assayed on 20 days by 4 different operators using different reagent lots. Total precision ranged from 5.3 to 16.6% CV and within run precision ranged from 2.4 to 10% CV.

b. Linearity/assay reportable range:

Different control samples with different levels of PCT were diluted serially in zero serum. Calculations of % deviation were made in relation to the mean of each expected concentration. Linear regression analysis was performed in accordance with NCCLS EP 6-P, "Evaluation of the Linearity of Quantitative Analytical Methods." Linearity of diluted samples was acceptable over the whole concentration range.

The Hook effect was examined using sera with extremely high levels of PCT in the BRAHMS PCT LIA. The high dose hook effect was observed in concentrations above 900ng/ml and is acceptable for the assay, since the highest standard is 400-600ng/ml.

c. Traceability, Stability, Expected values (controls, calibrators, or methods):

Standards (recombinant PCT) are provided in a range between 0.08 – 500 ng/ml. Identity and purity were verified by N-terminal amino acid sequencing (Edmanns) and mass analysis.

d. Detection limit:

The functional assay sensitivity (FAS) was determined to be 0.3 ng/ml.

The analytical sensitivity is 0.1 ng/ml. It was calculated by pipetting the standards 10 fold in the Brahms PCT LIA, calculating the mean of the RLUs and the standard deviation of the RLUs, adding 2 standard deviations to the mean of the lowest standard and reading the resulting RLU value off the PCT standard curve.

e. Analytical specificity:

The following substances were evaluated in the BRAHMS PCT LIA at the concentrations listed and were found not to affect test performance.

Interfering Substance	Non-Interfering Concentration
Bilirubin (conjugated)	40 mg/dl
Triglyceride	634 mg/dl
Hemoglobin	500 mg/dl
Protein (Albumin)	1 g/dl
Imipenem	1.18 mg/ml
Cefotaxim	90 mg/dl
Vancomycin	3.5 mg/ml
Dopamine	13 mg/dl
Noradrenaline	2 µg/ml
Dobutamine	11.2 µg/ml
Heparin	8000 U/l
Furosemide	2 mg/dl
Calcitonin	8 ng/ml
Katacalcin	30 ng/ml
a-CGRP*(calcitonin gene related peptide)	30 ng/ml
ß-CGRP*(calcitonin gene related peptide)	30 ng/ml
Calcitonin Salmon	30 µg/ml
Calcitonin Eel	30 µg/ml

f. Assay cut-off:

The assay cut offs are as follows: PCT level >2 ng/ml indicates a high risk of progression to severe sepsis and/or septic shock. PCT level < 0.5 ng/ml indicates a low risk of progression to severe sepsis and/or septic shock. Levels between 0.5 and 2.0 ng/ml are to be reviewed carefully taking into account the specific clinical background and condition of the individual patient, since PCT can be induced by non infectious conditions.

2. Comparison studies:

   a. *Method comparison with predicate device:*

      N/A

   b. *Matrix comparison:*

      Serum and plasma samples were tested with the BRAHMS PCT LIA. Ten patient specimens were tested in triplicate using serum tubes, heparin plasma tubes, EDTA plasma tubes and citrate plasma tubes. A difference was noted between the use of glass and plastic collecting tubes. For plastic tubes, a slight increase was noted if the sample remained in the collecting tube for more than 24 hrs, if the filling volume was higher or if plasma was used. The appropriate warnings have been stated under Specimen Collection and Preparation in the package insert.

3. Clinical studies:

   a. *Clinical Sensitivity:*

      N/A

   b. *Clinical specificity**:***

      N/A

   c. Other clinical supportive data (when a. and b. are not applicable):

Clinical data for the Brahms PCT LIA was obtained in 2 independent, controlled prospective studies performed in the ICU's of academic hospital settings. The data is summarized in the following graph and tables which shows the PCT results for SIRS and Sepsis compared to Severe sepsis and Septic shock on the 1st day of ICU admission. Study 1 consisted of 101 consecutive critically ill patients from a medical ICU in Switzerland. The median age was 59 years. There were 55 men and 46 women in the study. Study II consisted of 78 consecutive critically ill patients admitted to a medical and surgical ICU in Switzerland, including neutropenic and immunosuppressed patients. There were 57 men and 21 women in the study.

PCT by no infection or SIRS, Sepsis versus Severe Sepsis or Septic Shock
Cut Off 0.5 ng/ml

PCT Result Mueller*	**No infection or SIRS/Sepsis**	**Severe Shock/ Septic Shock**	**Totals**
PCT < 0.5	36	0	36
PCT > 0.5	34	31	65

Totals	70	31	101
PCT Result Harbarth**	**SIRS/Sepsis**	**Severe Shock/ Septic Shock**	**Totals**
PCT < 0.5	8	0	8
PCT > 0.5	24	46	70
Totals	32	46	78

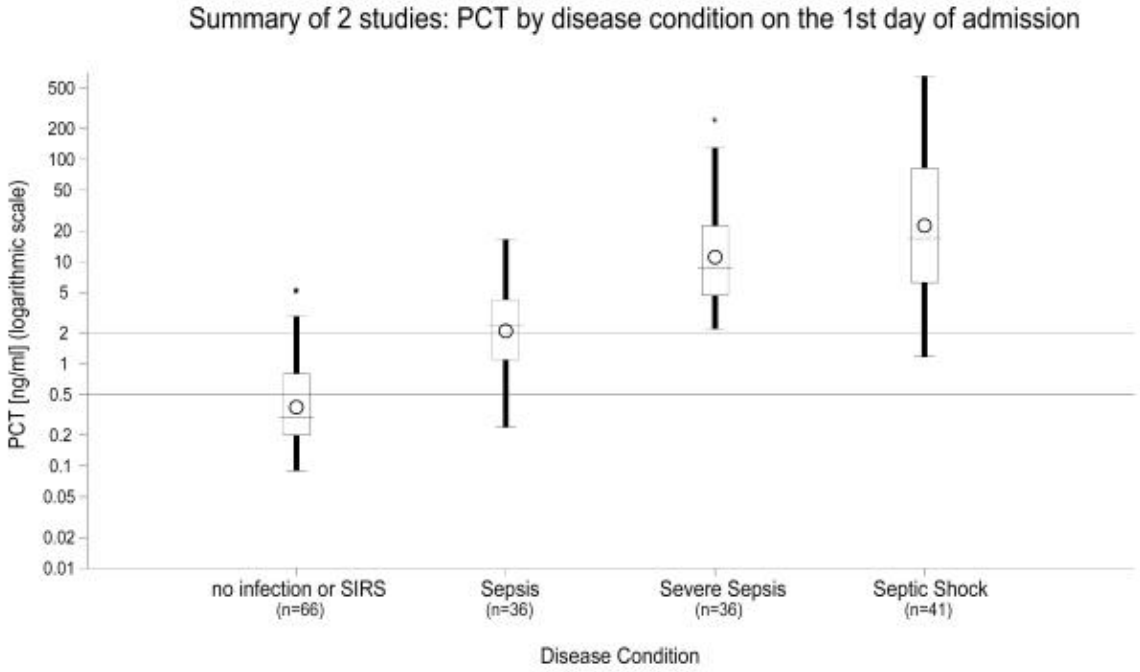
PCT by no infection or SIRS, Sepsis versus Severe Sepsis or Septic Shock
Cut Off 2.0 ng/ml

PCT Result Mueller*	**No infection or SIRS/Sepsis**	**Severe Shock/ Septic Shock**	**Totals**
PCT < 2.0	60	0	60
PCT > 2.0	10	31	41
Totals	70	31	101
PCT Result Harbarth**	**SIRS/Sepsis**	**Severe Shock/ Septic Shock**	**Totals**
PCT < 2.0	19	1	20
PCT > 2.0	13	45	58
Totals	32	46	78

**Muller Study (Day of ICU admission, Mean result of a duplicate run)*
Total of 101 critically ill patients (consecutive admission).

***Harbarth Study (Day of ICU admission, Mean result of a duplicate run)*
Total of 78 with clinically suspected infection

The 4 box and whisker diagrams below summarize the individual PCT results of the 4 subgroups of patients on the first day of ICU admission.



4. Clinical cut-off**:**

   See assay cut off above

5. Expected values/Reference range:

   In normal subjects PCT concentrations are < 0.3 ng/ml. In 144 healthy subjects tested with the BRAHMS PCT LIA, 143 had a PCT value < 0.3 ng/ml.

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.